Besides several changes in HAART were needed due to resistance or persisting replication. After the last change in HAART (darunavir-ritonavir),voriconazole C_0 decreased to 0.25 mg/L (50% decrease). Eventually, ranitidine was replaced by esomeprazole 40 mg IV BID. Three days later, voriconazole C_0 increased 14-fold and voriconazole dose could be reduced by 50% to 100 mg (2.5 mg/kg) BID. There were no other medication changes. Subsequent voriconazole C_0 stayed within the therapeutic range.

Results: Voriconazole systemic exposure depends on various factors among which CYP 450 activity influenced by genetic polymorphisms and DDI. Our patient was heterozygous for the *CYP2C19*17* variant allele, which has been associated with lower voriconazole AUC compared with wild-type individuals. However, her phenotype indicated a reduced activity of CYP2C19.

The change in voriconazole concentrations cannot be explained by a DDI with another drug of the antiretroviral treatment.

Conclusion: We report the case of an HIV patient with disseminated fungal disease who achieved targeted voriconazole C_0 using esomeprazole as a "booster" to overcome an ultrarapid CYP2C19*17/*1 genotype and a treatment by a CYP2C19 inducer such as ritonavir. Further evaluation is warranted for this "boosting strategy" to define the right booster dose, the relevance of this effect in rapid metabolizers and eventually transferability in clinical setting.

Disclosure of Interest: None declared.

PP135—PHARMACOMETABOLOMICS FOR INDIVIDUALIZED TREATMENT OF ALCOHOLISM: HIGH SERUM GLUTAMATE LEVEL IS ASSOCIATED WITH POSITIVE RESPONSE TO ACAMPROSATE TREATMENT

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Introduction: Acamprosate, a homo-taurine analogue, is approved for treatment of alcohol dependence. Meta-analyses favor acamprosate for its ability to support abstinence, which is the most stable type of remission in alcoholics. Yet, only a limited number of treatment-seeking alcoholics use acamprosate, most likely because of individual differences in response and the lack of response predictors.

Patients (or Materials) and Methods: We used a pharmacometabolomics approach to investigate metabolic response in serum amino acid metabolites (including acamprosate) between responders and nonresponders to acamprosate treatment. Serum samples were collected before and after 3 months of acamprosate treatment. Efficacy was defined by self-reported abstinence during acamprosate treatment and average γ-glutamyl transferase (GGT) levels at baseline and 3-month follow-up were used to confirm abstinence. Of those, 14 responders and 18 nonresponders comprised an investigation cohort and an additional 30 responders and 28 nonresponders comprised a replication sample.

Results: Initial metabolite screening was conducted using 32 alcohol-dependent subjects. Glutamate levels were significantly higher at baseline in the 14 responders compared with the 18 nonresponders [$t(30) = 2.7$, $P < 0.05$]. After acamprosate treatment, serum glutamate levels in the responder group significantly decreased compared with baseline [$t(26) = 3.3$, $P < 0.05$). Similarly, in a replication sample of 58 additional alcohol-dependent subjects, responders had significantly higher glutamate levels at baseline compared with the nonresponder group [$t(88) = 2.8$, $P < 0.05$], which decreased significantly after acamprosate treatment [$t(86) = 3.6$, $P < 0.05$].

Conclusion: Our findings suggest that high glutamate levels may be a biomarker to predict the efficacy of acamprosate treatment in alcohol-dependent subjects.

Disclosure of Interest: None declared.

PP136—GENETIC POLYMORPHISM OF CYP2D6 SIGNIFICANTLY AFFECTS THE PHARMACOKINETICS OF TOLPERISONE

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Introduction: Tolperisone, a centrally acting muscle relaxant, is used for relieving spasticity of neurological origin and muscle spasm associated with painful locomotor diseases. Tolperisone is mainly metaolized by CYP2D6 and CYP2C19, CYP1A2, and CYP2B6 are also involved in the metabolism of tolperisone. CY2D6 is responsible for variablility of drug response, largely due to genetic polymorphism. Therefore, we investigated the effects of *CYP2D6* genetic polymorphism on the pharmacokinetics of tolperisone.

Patients (or Materials) and Methods: Thirty healthy Korean subjects were selected and they were divided into 3 different groups according to *CYP2D6* genotype, *CYP2D6*wt/*wt (*wt= *1* or **2*, n = 10), *CYP2D6*wt/*10* (n = 10) and *CYP2D6*10/*10* (n = 10). After overnight fasting, each subject received a single 150-mg oral dose of tolperisone. Blood samples were collected up to 12 hours after drug intake, and plasma concentrations of tolperisone were determined by using LC-MS/MS analytical system.

Results: C_{max} and AUC_{inf} of tolperisone in *CYP2D6*10/*10* genotype group was significantly higher than those in *CYP2D6*wt/*wt* group ($P = 0.0007$ and $P = 0.0002$, respectively). Apparent oral clearance (CL/F) of tolperisone in *CYP2D6*wt/*10* and *CYP2D6*10/*10* group was 64% and 75% lower than that in *CYP2D6*wt/*wt* group ($P < 0.001$ and $P = 0.0001$, respectively). Among 3 genotypes, differences in $t_{1/2}$ of tolperisone were not statistically significant.

Conclusion: Tolperisone is mainly metabolized by *CYP2D6* and *CYP2D6* genetic polymorphism has a significant impact on the pharmacokinetics of tolperisone.

Disclosure of Interest: None declared.

PP137—EFFECTS OF THE GENETIC POLYMORPHISMS OF HUMAN MULTIDRUG AND TOXIN EXTRUSION 1 (HMATE1/SLC47A1) TRANSPORTER ON THE RENAL TUBULAR SECRETION OF N1-METHYLNICOTINAMIDE

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Introduction: Human multidrug and toxin extrusion 1 (hMATE1/*SLC47A1*) transporter may be involved in the active elimination clearance of many cationic drugs in the kidneys. Scarcity of knowledge about endogenous substrates of hMATE1 appears to hinder exploration of the roles of genetic polymorphisms on the functional activity of hMATE1.

Patients (or Materials) and Methods: Fifty-four healthy volunteers (32 males and 22 females; 23 [2] years) underwent 3-hour timed-urine collection and blood drawing at the midpoint. Plasma and urinary levels of N_1-methylnicotinamide (MNA) and creatinine were measured with a liquid chromatography-mass spectrometry system. Renal tubular secretion clearance of MNA ($C_{LTS,MNA}$) was calculated by subtracting the renal clearance of creatinine (a substitution of glomerular filtration rate) from that of MNA. Genetic variants of hMATE1/*SLC47A1* and another renal cation transporter, hOCT2/*SLC22A2*, were genotyped by polymerase chain reaction followed by direct sequencing. The protocol of the present study was

approved by the institutional review board, and written informed consent was obtained from each subject before the study.
Results: Plasma concentration of MNA, renal creatinine clearance, and CLTS,MNA were 9.9 (8.1) ng/mL, 139 mL/min/1.66 m^2, and 181 (110) mL/min/1.66 m^2, respectively, indicating that the tubular secretion of MNA is involved in its renal clearance. Eight SNPs, –151C>A, –66T>C, 191G>A, 373C>T, 708C>T, 1490G>C, IVS5–12G>C, and IVS5–4G>A, were detected on *SLC47A1* gene with minor allele frequencies of 0.009, 0.194, 0.009, 0.009, 0.083, 0.009, 0.343, and 0.463, respectively. A loss-of-function allele of *SLC22A2,* 808G>T, was detected with minor allele frequency of 0.105 and 1 subject was found having this variant as homozygote. She showed almost null $CL_{TS,MNA}$; therefore, this subject was excluded from the analysis. Seventeen subjects having either –66C/C or T/C alleles showed a trend toward reduced $CL_{TS,MNA}$ compared with those having the wild-type genotype (151 [IQR, 107–167] vs 184 [115–227] mL/min/1.66 m^2; $P = 0.08$). Other variants showed no appreciable effects on $CL_{TS,MNA}$.
Conclusion: We consider that $CL_{TS,MNA}$ may be a useful biomarker of the activity of renal organic cation transporters. The –66C allele of hMATE1/*SLC47A1* may contribute to reduced renal clearance of MNA in healthy subjects not having homozygous 808G>T variant of hOCT2/*SLC22A2*.
Disclosure of Interest: None declared.

PP138—ANALYSIS OF CYP2D6 GENETIC POLYMORPHISMS IN MEXICAN MESTIZOS, LACANDONES AND TZELTALES

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Introduction: More than 80 allelic variants have been described for *CYP2D6* that result in poor (PM), efficient or extensive (EM) and ultrarapid (UM) metabolizers of CYP2D6 drug substrates. The distribution of PMs, Ems, and UMs varies markedly among human populations; however, it has been particularly difficult to determine in countries with wide ethnic diversity. Currently, the Mexican population is composed of Mestizos (≈90%) and >85 different ethno linguistic indigenous populations (Mexican-Amerindians). Lacandones and Tzeltales are Mexican indigenous individuals that inhabit the state of Chiapas.
Aim: To perform a genetic analysis of *CYP2D6* to determine the frequency of the hypothetical PM and UM status in Lacandones, Tzeltales, and 2 mestizo populations and compare it with previously reported Mexican populations.
Patients (or Materials) and Methods: The *CYP2D6* genotype was analyzed in 154 Mexican Lacandones (ML), 26 Tzeltales (MT), 249 Mexican Mestizos from Central Mexico (MM1), and 100 Mexican Mestizos from Chiapas (MM2) healthy volunteers. All participants gave informed consent before its participation. The study was approved by the local ethical committee. Genomic DNA was extracted from blood samples by standard techniques. *CYP2D6* genotyping was performed by PCR for *CYP2D6*5* and multiplication alleles, TaqMan® assays (AB) were used for *CYP2D6*2, *3, *4, *6, *10, *17, *35, *41* and copy number variations. Differences in *CYP2D6* allele frequencies were compared by using the chi-square ($\chi 2$) test and/or Fisher's exact test. Statistical analysis was done by STATISTICA 4.3 and GraphPad Prism 3.02 softwares.
Results: The PM frequency was very low in MM1 (0.8%) and MM2 (1%), while it was absent from MLs and MTs in a manner similar to 0% previously found in Tepehuanos and in other Mexican Amerindian populations. The UM phenotype frequency in MLs was also very similar to Tepehuanos (1.3% and 1.5%, respectively) and to Mexican American populations previously studied. In MTs the UM frequency was 0%, while MM1 and MM2 showed a 5.6% and 3.0 frequency, respectively.
Conclusion: These data indicate that the frequencies of *CYP2D6* PM and UM predicted phenotypes are very similar between Tepehuanos, Lacandones, and Tzeltales, but differ from Mexican Mestizos from Central and Southeastern Mexico. The predicted PM phenotype was very similar between MM from Central and Southeastern Mexico but varied in the frequency of UM. These findings reveal Mexican populations diversity that could have important implications in drug response to CYP2D6 substrates.
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PP139—ASSOCIATION OF ABCB1, ABCC2, CYP2C9 AND CYP2C19 POLYMORPHISM WITH PHENYTOIN PLASMA CONCENTRATIONS

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Introduction: Epilepsy is the most prevalent chronic neurologic disorder that affects 65 million people worldwide. Phenytoin (PHT) is 1 of the most widely prescribed antiepileptic drugs (AEDs); however, large interindividual variability in doses and concentrations has been observed in epilepsy treatment with PHT. Functional polymorphisms in genes encoding drug-metabolizing enzymes, drug transporters, and drug targets have been suggested to contribute to this genetic variability.
Aim: To evaluate the association of *CYP2C9*, *CYP2C19*, *ABCB1*, and *ABCC2* polymorphism on PHT plasma levels in epileptic patients.
Patients (or Materials) and Methods: The present investigation was carried out in 57 consecutive patients (16–65 years) suffering epilepsy and treated with phenytoin. Approval from the institutional biomedical research ethics committee and the informed consent of patients was obtained before enrollment into the study. Genomic DNA was isolated from blood samples by standard technique. Genotyping of *CYP2C9*2, CYP2C19*2* and **3, ABCB1 C1234T, C3435T, G2677A/T, ABCC2 G24A,* and *G1249A* was performed by real-time